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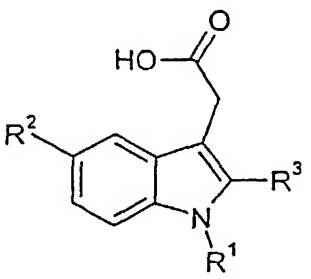
(54) Title: USE OF INDOLE-3-ACETIC ACIDS IN THE TREATMENT OF ASTHMA, COPD AND OTHER DISEASES



(I)

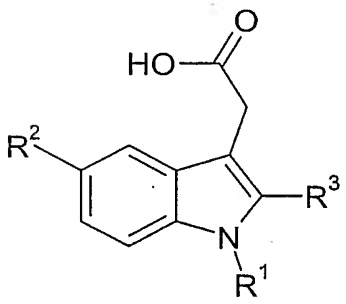
(57) Abstract: The invention relates to N-substituted indole-3-acetic acid derivatives of the general formula in which R^1 is optionally substituted benzothiazolyl, pyrimidin-4-yl, imidazol-2-yl, oxazol-2-yl or thiazol-2-yl, R^2 is hydrogen, halogen, C_{1-6}alkyl or C_{1-6}alkoxy and R^3 is hydrogen or C_{1-6}alkyl (see further details in the description), and their use in the treatment of respiratory diseases such as asthma, rhinitis and chronic obstructive pulmonary disease (COPD), and other diseases mediated by prostaglandin D2(PGD2).

Use of indole-3-acetic acids in the treatment of asthma, COPD and other diseases.

The present invention relates to a new pharmaceutical use for certain indole acetic acids.

EPA 1 170 594 discloses methods for the idntification of compounds useful for the treatment of disease states mediated by prostaglandin D2, a ligand for orphan receptor CRTH2. GB 1356834 discloses a series of compounds said to possess anti-inflammatory, analgesic and antipyretic activity. It has now surprisingly been found that certain compounds within the scope of GB 1356834 are active at the CRTH2 receptor, and as a consequence are expected to be potentially useful for the treatment of various respiratory diseases, including asthma and COPD.

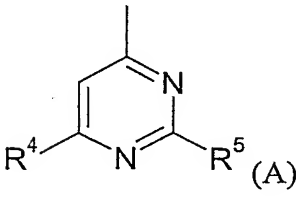
In a first aspect the invention therefore provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the treatment of asthma and COPD:



(I)

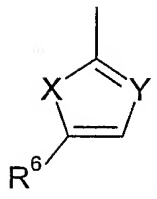
in which

R^1 is a 1,3-benzothiazole group optionally substituted by halogen, C_{1-6}alkyl, C_{1-6}alkoxy or a group of formula (A) or (B):



(A)

where R^4 and R^5 are independently halogen, C_{1-6}alkyl, C_{1-6}alkoxy, phenoxy optionally substituted by halogen, C_{1-6}alkyl, C_{1-6}alkoxy



(B)

where one of X and Y is nitrogen and the other is nitrogen, oxygen or sulphur and R^6 is phenyl optionally substituted by substituted by halogen, C_{1-6}alkyl, C_{1-6}alkoxy;
R^2 is hydrogen, halogen , C_{1-6}alkyl, C_{1-6}alkoxy, and
R^3 is hydrogen, C_{1-6}alkyl.

The term alkyl, whether alone or as part of another group, includes straight chain and branched chain alkyl groups.

Preferably R^1 is a 1,3-benzothiazole group, or a group of formula (A). The groups R^4 and R^5 can be the same or different. Preferably R^4 and R^5 are both propoxy, chloro or phenoxy.

Preferably R^2 is methyl or methoxy.

Preferred compounds of the invention include:
[1-(2,6-diphenoxypyrimidin-4-yl)-2,5-dimethyl-1H-indol-3-yl]acetic acid,
[1-(2,6-diphenoxypyrimidin-4-yl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid,
[1-(2,6-diisopropoxypyrimidin-4-yl)-2,5-dimethyl-1H-indol-3-yl]acetic acid,
[5-methoxy-2-methyl-1-(6-methyl-2-phenylpyrimidin-4-yl)-1H-indol-3-yl]acetic acid,
[1-(2,6-dichloropyrimidin-4-yl)-2,5-dimethyl-1H-indol-3-yl]acetic acid,
[1-(1,3-benzothiazol-2-yl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid,
and pharmaceutically acceptable salts thereof.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

Certain compounds of formula (I) are believed to be novel and form a further aspect of the invention.

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine, or an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of CRTh2 receptor activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of PGD_2 and its metabolites. Examples of such conditions/diseases include:

(1) **(the respiratory tract)** obstructive airways diseases including: asthma (such as bronchial, allergic, intrinsic, extrinsic and dust asthma particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness)); chronic obstructive pulmonary disease (COPD)(such as irreversible COPD); bronchitis (including eosinophilic bronchitis); acute, allergic, atrophic rhinitis or chronic rhinitis (such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca), rhinitis medicamentosa, membranous rhinitis (including croupous, fibrinous and pseudomembranous rhinitis), scrofoulous rhinitis, perennial allergic rhinitis, easonal rhinitis (including rhinitis nervosa (hay fever) and vasomotor rhinitis); nasal polyposis; sarcoidosis; farmer's lung and related diseases; fibroid lung; idiopathic interstitial pneumonia; cystic fibrosis; antitussive activity; treatment of chronic cough associated with inflammation or iatrogenic induced ;

(2) **(bone and joints)** arthrides including rheumatic, infectious, autoimmune, seronegative, spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin and eyes)** psoriasis, atopical dermatitis, contact dermatitis, other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, chronic skin ulcers, uveitis, Alopecia areatacorneal ulcer and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease; food-related allergies which have effects remote from the gut, (such as migraine, rhinitis and eczema);

(5) **(central and peripheral nervous system)** Neurodegenerative diseases and dementia disorders (such as Alzheimer's disease, amyotrophic lateral sclerosis and other motor neuron diseases, Creutzfeldt-Jacob's disease and other prion diseases, HIV encephalopathy (AIDS dementia complex), Huntington's disease, frontotemporal dementia, Lewy body dementia and vascular dementia), polyneuropathies (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy), plexopathies, CNS demyelination (such as multiple sclerosis, acute disseminated/haemorrhagic encephalomyelitis, and subacute sclerosing panencephalitis), neuromuscular disorders (such as myasthenia gravis and Lambert-Eaton syndrome), spinal diorders (such as tropical spastic paraparesis, and stiff-man syndrome), paraneoplastic syndromes (such as cerebellar degeneration and encephalomyelitis), CNS trauma, migraine and stroke.

(6) **(other tissues and systemic disease)** atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus; systemic lupus, erythematosus; Hashimoto's thyroiditis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, idiopathic thrombocytopenia pupura; post-operative adhesions, sepsis and ischemic/reperfusion injury in the heart, brain, peripheral limbs hepatitis (alcoholic, steatohepatitis and chronic viral) , glomerulonephritis, renal impairment, chronic renal failure and other organs

(7) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(8) Diseases associated with raised levels of PGD_2 or its metabolites.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

Preferably the compounds of the invention are used to treat diseases in which the chemokine receptor belongs to the CRTh2 receptor subfamily.

Particular conditions which can be treated with the compounds of the invention are asthma, rhinitis and other diseases in which raised levels of PGD_2 or its metabolites. It is preferred that the compounds of the invention are used to treat asthma.

Novel compounds of formula (I) form a further aspect of the invention. Preferred compounds are those named above and exemplified herein.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a further aspect, the present invention provides the use of a compound or formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy in combination with drugs used to treat asthma and rhinitis (such as inhaled and oral steroids, inhaled β2-receptor agonists and oral leukotriene receptor antagonists).

The invention still further provides a method of treating a disease mediated by prostaglandin D2, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

The invention also provides a method of treating a respiratory disease, such as athma and rhinitis, especially asthma, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compound of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compound of the invention is administered orally.

Experimental Section

Example 1
Preparation of [5-methoxy-2-methyl-1-(6-methyl-2-phenylpyrimidin-4-yl)-1H-indol-3-yl]acetic acid

Step (a): Preparation of ethyl [5-methoxy-2-methyl-1-(6-methyl-2-phenylpyrimidin-4-yl)-2,3-dihydro-1H-indol-3-yl]acetate.

To ethyl (5-methoxy-2-methyl-2,3-dihydro-1H-indol-3-yl)acetate (2.0g) in ethanol was added 4-chloro-6-methyl-2-phenylpyrimidine (1.76g) followed by conc. HCl (0.5mL) and the reaction was heated at reflux for 24 hrs. Solvent was evaporated, water was added, reaction was neutralized to pH 7, and product extracted with ethyl acetate. This gave the sub-title compound (3.4g). This was used without further purification in the next step.

Step (b): Preparation of ethyl [5-methoxy-2-methyl-1-(6-methyl-2-phenylpyrimidin-4-yl)-1H-indol-3-yl]acetate

To the product of example 1 step (a) (4.7g) in diphenyl ether (40mL) was added 10%Pd/C (2.3g) and reaction heated to reflux for 5 hrs. The reaction mixture was filtered through celite. Evaporation of solvent and purification by Flash silica chromatography using a gradient eluent system (10% diethylether/90% hexane to 40% diethylether/60%hexane) gave the sub-title compound (1.6g).

Step (c): Preparation of [5-methoxy-2-methyl-1-(6-methyl-2-phenylpyrimidin-4-yl)-1H-indol-3-yl]acetic acid

To the product of example 1 step (b) (1.6g) in ethanol (40mL) was added NaOH (0.5g) and the heated at reflux for 30mins. Solvent was evaporated and water (50mL) added. The solution was then acidified to pH 5 with dilute HCl. The resultant solid was filtered, dried and recrystallized ($EtOH/H_2O$) to give the title product as a solid (0.9g).

Melting Point: 160-162°C
APCI+ (M+H) = 388

Example 2

Preparation of [1-(1,3-benzothiazol-2-yl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

Prepared in a similar manner to Example 1.

Melting Point: 158-160°C
APCI+ (M+H) = 353

Example 3

Preparation of [1-(2,6-diphenoxypyrimidin-4-yl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

Step (a): 2,4-dichloro-6-[1-(4-methoxyphenyl)hydrazino]pyrimidine

To a solution of anhydrous sodium acetate (63.1g) in water (260mL) was added EtOH (1200mL). To this was added (4-methoxyphenyl)hydrazine (59g) and 2,4,6-trichloropyrimidine (78.5g). The reaction was shaken until all in solution. The reaction was left to stand for 2hrs and the resultant solid filtered, washed with EtOH and dried in vacuo. Recrystallisation from EtOH/$CHCl_3$ gave the sub-title compound (20g).

Melting point : 156-158°C

Step (b): Preparation of [1-(2,6-dichloropyrimidin-4-yl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

To a solution of the product of example 3 step (a) (20g) in 4-oxopentanoic acid (65mL) was bubbled HCl gas. The solid precipitated from solution after 5 mins. The reaction was left for 2hrs. The reaction mixture was poured onto water (750mL) and stirred vigorously for 45 mins. The solid was filtered and recrystallized from EtOH. This gave the sub-title compound as solid (14.1g)

Melting Point: 201-202°C

Step (c): Preparation of [1-(2,6-diphenoxypyrimidin-4-yl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

To a solution of phenol (0.85g) dissolved in 1,2-dimethoxyethane (30mL) was added sodium (0.21g). The reaction was heated until no more sodium dissolved. To this reaction was then added the product of example 3 step (b) (1.1g) dissolved in 1,2-dimethoxyethane (25mL) over 10 mins. The reaction was stirred for 1 hr and then heated at reflux for 1 hr. Solvents were evaporated and water (100mL) and ethyl acetate (50mL) added. Dilute HCl was added until the mixture reached pH 2. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated in vacuo. Recrystallisation using toluene gave the title compound as s solid (0.77g)

Melting Point: 168-170°C
APIC+ (M+H) = 482

Example 4

Preparation of [1-(2,6-diphenoxypyrimidin-4-yl)-5-methyl-1H-indol-3-yl]acetic acid.

Prepared in a similar manner to Example 3.
APIC+ (M+H) = 466

Example 5

Preparation of [1-(2,6-diisopropoxypyrimidin-4-yl)-5-methyl-1H-indol-3-yl]acetic acid.

Prepared in a similar manner to Example 3.
APCI+ (M+H) = 398

Other compounds of formula (I) can be prepared according to the procedures outlined in GB 1356834.

Pharmacological Data

Intracellular calcium mobilisation

Human Embryonic Kidney Cells co-transfected with both the CRTh2 receptor and Gα16 G-protein (HEK-hrCRTh2-Gα16) are routinely cultured as monolayers in Dulbecco's Modified Eagles Medium (DMEM; Sigma) supplemented with 10% (v:v) heat inactivated foetal bovine serum (New Zealand sourced; Hyclone), 1% (v:v) non-essential amino acids (Gibco BRL), 1% (v:v) penicillin/streptomycin (Gibco BRL), 2mM L-glutamine (Gibco BRL) and grown under 1mg/ml (v:v) Geneticin (Gibco BRL) antibiotic selection.
Approximately 24 hours prior to the assay the cells are plated at a seeding density of 100,000 cells/well in 100µl growth media into black walled 96 well Poly-D-Lysine coated plates (Becton Dickinson), with clear bottoms to allow cell inspection and fluorescence measurements from the bottom of each well. All cultures are maintained under standard tissue culture conditions (37°C in a humidified atmosphere of 5% CO_2).

To enable changes in intracellular calcium levels to be measured in HEK-hrCRTh2-Gα16 cells fluo-3AM is utilised as the fluorescent calcium indicator. A dye loading buffer is prepared which consists of a final concentration of 5µM Fluo-3AM fluorescent cytoplasmic calcium indicator dye (Tef Labs), 2.2µl/ml Pluronic F127 (Molecular Probes) to promote dye uptake, and 0.5 mM brilliant black (Sigma) to reduce background fluorescence in Balanced Salt Solution (BSS; 125mM NaCl, 5.4mM KCl, 16.2mM $NaHCO_3$, 0.8mM $MgCl_2$, 1mM $CaCl_2$, 20mM HEPES, 1mM NaH_2PO4, 5.5mM D-(+)-Glucose, 0.1% BSA and pH 7.4 with NaOH). On the day of the assay, the cells are dye loaded in the dark for 60 min at 37°C by removing the existing growth media and adding 100µl of the dye loading buffer to each well.

Test compounds are made up at a stock concentration of 10mM in DMSO. The compounds to be evaluated are then prepared, by serial dilution in BSS buffer, to the required concentrations for inhibition dose response curves to be constructed. These dilutions are then placed into the 1st addition plate which is pre-warmed to 37°C prior to assay. A PGD_2 (Cayman Chemical) E/[A] curve is generated for each independent assay by measuring the flux of intracellular calcium in response to increasing agonist concentrations. This allows the potency agonist ($p[A]_{50}$) value to be determined for the HEK-hrCRTh2-Gα16 cells on any given day. Once the $p[A]_{50}$ for PGD_2 has been determined a separate assay plate containing 2 x $p[A]_{50}$ of PGD_2 is prepared as the 2nd addition plate (or agonist plate). This

PGD_2 plate is also pre-warmed to 37°C prior to assay. The inhibition curve data obtained is then fitted as described below to estimate an IC_{50} value (concentration of the test compound which produces 50% inhibition of the response to PGD_2).

Measurements of increases in intracellular Ca^{2+} ($[Ca^{2+}]_i$) are then made using a 96 well FLIPr. Fluorescence changes are measured after the addition of either the test AR-C compound on its own (1st addition plate) or the test compound (1st addition plate) followed by the reference agonist, PGD_2 (2nd addition plate).
Measurements of increases in intracellular Ca^{2+} ($[Ca^{2+}]_i$) are then made with the laser intensity set to a suitable level to obtain basal values of approximately 10,000 fluorescence units. To asses compound activity alone fluorescence readings are measured over 5 minutes (1st plate addition), then agonist is added and the compound activity in competition is assessed for a further 2 minutes. The maximum fluorescent signal generated by PGD_2 is typically greater than 15,000 units and obtained with 15 sec of addition.

Agonist Analysis:

Absolute fluorescence units for PGD_2 control E/[A] curve data are fitted to the following form of the Hill equation using a 4 parameter logistic curve fitting program,

$$E = \beta + \frac{(\alpha-\beta)[A]^m}{[A]^m + [A_{50}]^m} \qquad \text{Equation (1)}$$

in which α and β are the upper and lower asymptote respectively, and $[A]_{50}$ and m are the location and slope parameters respectively. Using the calculated α value, the absolute fluorescence units were subsequently expressed as a % of this value. For AR-C compounds that displayed agonism, the $p[A]_{50}$ was estimated as well as the intrinsic acitivity (α of test agonist/α of PGD_2).

Antagonist Analysis:

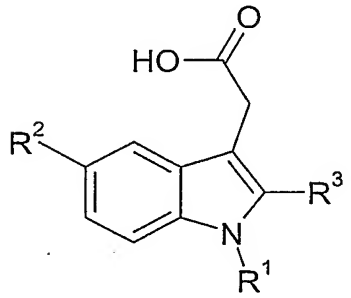
Antagonist affinity values were estimated using the pIC_{50} Cheng-Prusoff analysis. To this end a PGD_2 E/[A] curve was constructed (see above) and fitted to equation 1 to estimate the potency ($[A]_{50}$]) and slope (m) values. The effects of the test compound were then assessed against 2 x $p[A]_{50}$ concentration of the reference agonist, PGD_2. The inhibition

curve data obtained was subsequently fitted to equation 1 to estimate an IC_{50} value (concentration of the test compound which produces 50% inhibition of the response to PGD_2).

Compounds of formula (I) have a pA_2 value of less than (<) 10μM. Specifically [1-(2,6-diphenoxypyrimidin-4-yl)-2,5-dimethyl-1H-indol-3-yl]acetic acid has a $pA_2 = 6.8$, [5-methoxy-2-methyl-1-(6-methyl-2-phenylpyrimidin-4-yl)-1H-indol-3-yl]acetic acid has a $pA_2 = 6.5$ and [1-(1,3-benzothiazol-2-yl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid has a $pA_2 = 6.5$

CLAIMS

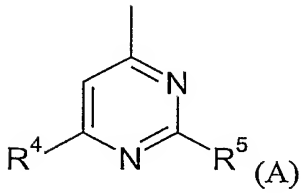
1. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the teatment of asthma nd COPD:



(I)

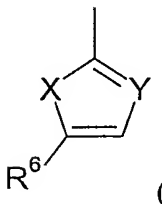
in which

R^1 is a 1,3-benzothiazole group optionally substituted by halogen, C_{1-6}alkyl, C_{1-6}alkoxy or a group of formula (A) or (B):



(A)

where R^4 and R^5 are independently halogen, C_{1-6}alkyl, C_{1-6}alkoxy, phenoxy optionally substituted by halogen, C_{1-6}alkyl, C_{1-6}alkoxy



(B)

where one of X and Y is nitrogen and the other is nitrogen, oxygen or sulphur and R^6 is phenyl optionally substituted by substituted by halogen, C_{1-6}alkyl, C_{1-6}alkoxy;

R^2 is hydrogen, halogen , C_{1-6}alkyl, C_{1-6}alkoxy; and

R^3 is hydrogen, C_{1-6}alkyl.

2. Use according to claim 1 in which R^1 is is a 1,3-benzothiazole group.

3. Use according to claim 1 or 2 in which R^1 is a group of formula (A).

4. Use according to claim 3 in which R^4 and R^5 are both propoxy, chloro or phenoxy.

5. Use according to any one of claims 1 to 4 in which R^2 is methyl or methoxy.

6. Use according to any one of claims 1 to 5 in which the compound of formula (I) is selected from:
[1-(2,6-diphenoxypyrimidin-4-yl)-2,5-dimethyl-1H-indol-3-yl]acetic acid,
[1-(2,6-diphenoxypyrimidin-4-yl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid,
[1-(2,6-diisopropoxypyrimidin-4-yl)-2,5-dimethyl-1H-indol-3-yl]acetic acid,
[5-methoxy-2-methyl-1-(6-methyl-2-phenylpyrimidin-4-yl)-1H-indol-3-yl]acetic acid,
[1-(2,6-dichloropyrimidin-4-yl)-2,5-dimethyl-1H-indol-3-yl]acetic acid,
[1-(1,3-benzothiazol-2-yl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid,
and pharmaceutically acceptable salts thereof.

7. A compound of formula (I) according to any one of claims 1 to 6 for use in therapy.

8. A method of treating a disease mediated by prostaglandin D2, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt as defined in claims 1 to 6.

9. A method of treating a respiratory disease, such as asthma and rhinitis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in claims 1 to 6.

10. A novel compound of formula (I).

11. A compound of formula (I) selected from:
[1-(2,6-diphenoxypyrimidin-4-yl)-2,5-dimethyl-1H-indol-3-yl]acetic acid,
[1-(2,6-diphenoxypyrimidin-4-yl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid,
[1-(2,6-diisopropoxypyrimidin-4-yl)-2,5-dimethyl-1H-indol-3-yl]acetic acid,
[5-methoxy-2-methyl-1-(6-methyl-2-phenylpyrimidin-4-yl)-1H-indol-3-yl]acetic acid,

[1-(2,6-dichloropyrimidin-4-yl)-2,5-dimethyl-1H-indol-3-yl]acetic acid,
[1-(1,3-benzothiazol-2-yl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid,
and pharmaceutically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00185

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/405, A61K 31/426, A61K 31/428, A61K 31/506, A61P 11/02, A61P 11/06, A61P 17/06, A61P 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA, BIOSIS, EMBASE, MEDLINE, EPO-INTERNAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1356834 A (IMPERIAL CHEMICAL INDUSTRIES LIMITED), 19 June 1974 (19.06.74), (analogues with anti-inflammatory activity) --	1-10
X	EP 1170594 A2 (PFIZER PRODUCTS INC.), 9 January 2002 (09.01.02), (analogous PGD2-antagonist with the exact same use - see especially example 9, page 22, lines 9-11 and 18-19 and fig. 10B (c), page 34	1-10
X	see also abstract; page 2, lines23-31 and page 4, lines 26-36) --	1-10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2003	21 -05- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer PER RENSTRÖM Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00185

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, file CAPLUS, CAPLUS accession no. 1978:500103, Document no. 89:100103, Cohn, Martin A. et al: "Failure of hypoxic pulmonary vasoconstriction in the canine asthma model. Effect of prostaglandin inhibitors"; & J. Clin. Invest. (1978), 61(6), 1463-70, (an analogous prostaglandin inhibitor, indomethacin, with anti-asthmatic effects)	1-10
	--	
X	EP 0499143 A2 (HOECHST AKTIENGESELLSCHAFT), 19 August 1992 (19.08.92), (non-steroidal anti-inflammatorydrugs, e.g. indomethacin, by inhalation, for the treatment of asthma - abstract; claims 3 and 8	1-10
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X	STN International, file CAPLUS, CAPLUS accession no. 2000:748811, Document no. 133:291110, Tanabe, Yosuke: "Indomethacin for treatment of psoriasis"; & JP,A2,2000297037, 20001024	7
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X	STN International, file CAPLUS, CAPLUS accession no. 1980:437283, Document no. 93:37283, Kabata, Masayuki: "Effect of cutaneous prostaglandins and anti-inflammatory agents on some experimental dermatitides"; & Hirosaki Igaku (1979), 31(4), 597-611	7
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X	STN International, file CAPLUS, CAPLUS accession no. 1982:210573, Document no. 96:210573, Holdstock G. et al: "Increased suppressor cell activity in inflammatory bowel disease"; & Gut (1981), 22(12), 1025-30	7
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A	US 5965582 A (LEBAUT ET AL), 12 October 1999 (12.10.99), related compounds with anti-asthmatic and anti-inflammatory effects	1-10
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/00185

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-6,8-9
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet*

2. ☒ Claims Nos.: 8
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet**

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

*
Claims 1-6,8-9 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule. 39.1.(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

**

The expression "a disease mediated by prostaglandin D2" may relate to a number of different disorders and conditions which can not be clearly defined by this expression. The claim is in violation with the requirement of Article 6 PCT that claims shall be clear and concise. The search has therefore been limited to certain examples of such diseases, such as asthma, rhinitis and COPD.

INTERNATIONAL SEARCH REPORT

Information on patent family members

29/04/03

International application No.
PCT/SE 03/00185

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		AR 203626 A	30/09/75
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		AT 100174 A	15/06/75
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		CA 983932 A	17/02/76
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INTERNATIONAL SEARCH REPORT

Information on patent family members

29/04/03

International application No.
PCT/SE 03/00185

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